REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Percutaneous transluminal angioplasty versus primary stenting in infrapopliteal arterial disease: A meta-analysis of randomized trials

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Background: **Percutaneous transluminal angioplasty (PTA) and primary stenting are commonly used endovascular therapeutic procedures for the treatment of infrapopliteal arterial occlusive disease. However, which procedure is more beneficial for patients with infrapopliteal arterial occlusive disease is unknown.**

Methods and Results: **We performed a meta-analysis, searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and relevant websites without language or publication date restrictions for randomized trials that compared primary stenting with PTA in patients with infrapopliteal arterial occlusive disease. The keywords were "stents," "angioplasty," "infrapopliteal," "tibial arteries," and "below knee." We selected immediate technical success, primary and secondary patency, limb salvage, and patient survival as the outcomes of this meta-analysis. On the basis of the inclusion criteria, we identified six prospective randomized trials. One-year outcomes did not show any significant differences between the PTA and primary stenting groups, respectively: technical success (93.3% vs 96.2%; odds ratio [OR], 0.59; 95% confidence interval [CI], 0.24-1.47; $P = .25$), primary patency (57.1% vs 65.7%; OR, 0.95; 95% CI, 0.35-2.58; $P = .92$), secondary patency (73.5% vs 57.6%; OR, 2.08; 95% CI, 0.81-5.34; $P = .13$), limb salvage (82.2% vs 87.5%; OR, 0.64; 95% CI, 0.29-1.41; $P = .27$), and patient survival (84.0% vs 87.5%; OR, 0.79; 95% CI, 0.40-1.55; $P = .49$).**

Conclusions: **For infrapopliteal arterial occlusive disease, primary stenting has the same 1-year benefits as PTA. There is insufficient evidence to support the superiority of either method. Primary stenting is associated with a trend toward higher primary patency and lower secondary patency. Further large-scale prospective randomized trials should produce more reliable results. (J Vasc Surg 2014;59:1711-20.)**

Infrapopliteal arterial occlusive disease afflicts numerous patients with pain at rest, ischemic ulceration, or gangrene.[1,2] Critical limb ischemia (CLI) mainly results from this disease. In general, patients suffering from CLI have many comorbidities, such as diabetes mellitus and end-stage renal disease, and often have high morbidity, mortality, and consumption of health care and social care resources.[3] Therefore, effectual management is urgently required for patients with CLI.

With the rapid improvements in endovascular instruments and experience of physicians, endovascular therapy has become a major option for the revascularization of infrapopliteal occlusive arteries. Percutaneous transluminal angioplasty (PTA) or primary stenting is the most commonly used endovascular therapy for this disease, especially during the initial onset of CLI. Currently, PTA is considered an effective treatment because of its minimal invasiveness, shortened hospitalization time, and acceptable patency rate.[4] However, the application of PTA is limited because of low procedural success, complications associated with the endovascular procedure, and relatively high restenosis rate.[5,6] Primary stenting, especially the use of dedicated stents that are specially designed for the infrapopliteal arteries, is being chosen more often to treat CLI due to infrapopliteal arterial disease. However, the role of stenting in the infrapopliteal arteries is still debated. The major concerns are the risks of fracture, restenosis, and thrombosis. Thus, treating infrapopliteal arterial occlusive disease remains a challenge for physicians. In recent years, several randomized studies have assessed the safety and efficacy of PTA vs primary stenting for CLI. However, the conclusions from these studies remain inconsistent, contributing to the ongoing controversy.

On the basis of this background, we performed this meta-analysis to assess the overall outcomes from all

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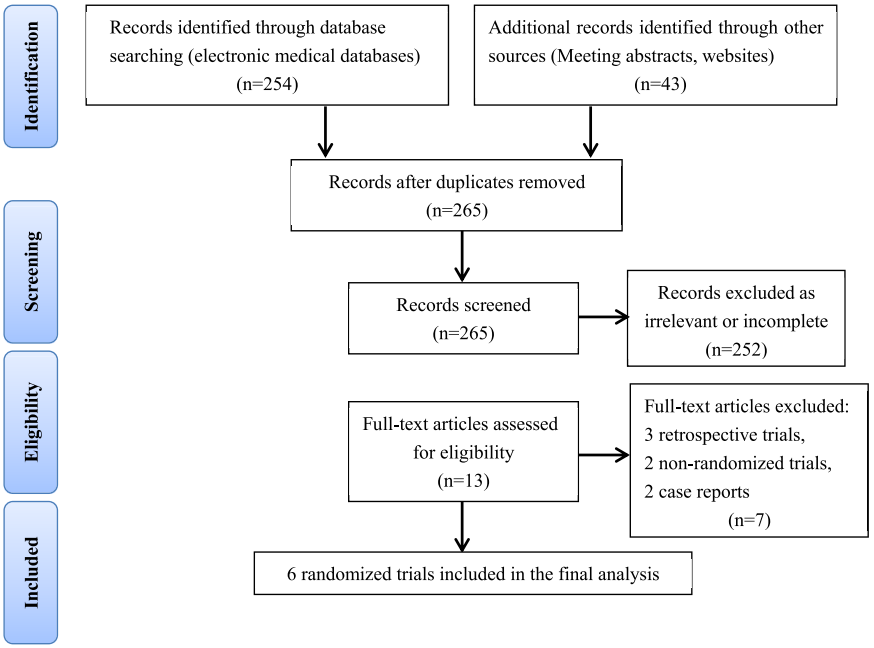

Fig 1. Flow chart of the literature search according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement.

randomized trials comparing the results of PTA vs primary stenting for infrapopliteal arterial occlusive disease.

METHODS

Eligibility criteria. We established a prespecified protocol for this meta-analysis. Eligible trials should fulfill the following criteria: (1) prospective randomized trial; (2) comparing PTA and primary stenting in infrapopliteal arterial occlusive disease; (3) minimum follow-up of 6 months; (4) intention-to-treat analysis; and (5) reporting at least one of the following outcomes: technical success, primary patency (at 6 or 12 months), secondary patency (at 6 or 12 months), limb salvage (at 6 or 12 months), and patient survival (at 6 or 12 months). We excluded reviews and studies that did not provide data to calculate summary statistics. Studies with incomplete data for demographic or clinical variables were still included.

Information sources and search strategy. We performed a systematic search of the literature according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7] The search was applied to PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and other relevant websites without language or publication date restrictions. Experts of this field were consulted, and professional inquiries were obtained. The medical subject headings and keywords used to identify relevant articles were "stents," "angioplasty," "infrapopliteal," "tibial arteries," and "below knee." The most recent search was performed in June 2013.

Study selection and assessment of risk of bias. One author screened the studies by title and abstract for inclusion. Identified articles were assessed independently by another author to confirm their eligibility. Those studies that qualified for full-text review were reviewed by two independent reviewers for inclusion in the analysis. The risk of bias was evaluated in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*[8] on the basis of the following methodologic items: sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. Any disagreements between the reviewers were arbitrated by discussion with the entire group.

Outcome variables. On the basis of the Society for Vascular Surgery/American Association for Vascular Surgery reporting standards for endovascular procedures,[9] we chose immediate technical success, primary and secondary patency, limb salvage, and patient survival as the outcomes of this meta-analysis.

Data extraction. A database sheet was developed, tested in three randomly selected studies, and then refined accordingly. We tried to collect all possible relevant information. One author extracted the data from the included studies, and another author double-checked the extracted data. The data abstracted included (1) clinical and demographic characteristics (age, male gender, diabetes mellitus, coronary artery disease, chronic kidney disease, smoking, hypertension, dyslipidemia, and angiographic follow-up) and (2) primary and secondary outcomes (technical success, loss to follow-up, primary patency, secondary patency, clinical improvement, limb salvage, and patient survival). Incomplete data were not pursued with the study authors.

Statistical analysis. The statistical analyses were performed on an intention-to-treat basis with use of

Table I. Bias risk assessment for six randomized trials using the Cochrane Collaboration's tool[a]

Domain	*Rand 2006*	*Bosiers 2009*	*Randon 2010*	*Brodmann 2011*	*Rand 2011*	*Scheinert 2012*
Sequence generation	Yes [Numbered envelopes]	Yes [Using a computer random number generator]	Yes [Computer-generated randomization sequence]	Yes [Computer-generated list]	Unclear [Insufficient information about the sequence generation]	Yes [Numbered envelope system]
Allocation concealment	Unclear [Insufficient information]	Yes [Numbered sealed envelopes]	Yes [Numbered sealed envelopes]	Yes [Numerated closed envelopes]	Unclear [Insufficient information]	Unclear [Insufficient information]
Blinding of participants, personnel, and outcome assessors	Yes [Incomplete blinding, but the outcome and the outcome measurement are not likely to be influenced]	Yes [Physicians and patients were unaware of the treatment group assignment]	Yes [Blinding of participants and key study personnel ensured; unlikely that the blinding could have been broken]	Yes [The blinding was warranted because of sealed envelopes]	Unclear [Insufficient information]	Unclear [Insufficient information]
Incomplete outcome data	Yes [Reasons for missing outcome data unlikely to be related to true outcome]	Yes [Reasons for missing outcome data unlikely to be related to true outcome]	Yes [No missing outcome data]	Yes [Reasons for missing outcome data unlikely to be related to true outcome]	Yes [Reasons for missing outcome data unlikely to be related to true outcome]	Yes [Reasons for missing outcome data unlikely to be related to true outcome]
Selective outcome reporting	Yes [Outcomes were predefined in the method section of the trial]	Yes [Outcomes were predefined in the method section of the trial]	Yes [All of the interested outcomes have been reported]	Yes [Outcomes were predefined in the method section of the trial]	No [One or more outcomes of interest are reported incompletely]	Yes [All of the interested outcomes have been reported]
Other sources of bias	Unclear [Insufficient information]	Unclear [Insufficient information]	Unclear [Insufficient information]	Unclear [Insufficient information]	Unclear [Insufficient information]	Unclear [Insufficient information]

[a]Explanation of judgment is provided in brackets. Yes indicates low risk of bias, no indicates a high risk of bias, and unclear indicates unknown risk of bias.

RevMan software (version 5.2, The Cochrane Collaboration) and Stata 11 statistical software (StataCorp, College Station, Tex). The odds ratio (OR) and 95% confidence interval (CI) were used as the summary statistics. Heterogeneity between studies was examined by the χ^2 test and inconsistency (I^2) statistic. P values $< .1$ indicated significant heterogeneity. I^2 values $<25\%$ indicated low heterogeneity, 25% to 50% indicated moderate heterogeneity, and $>50\%$ indicated high heterogeneity. The pooled ORs and 95% CI were calculated by the Mantel-Haenszel (M-H) fixed-effects model, unless significant heterogeneity existed, in which case the random-effects model was used. Publication bias was assessed by the funnel plot, Egger test, and Begg test. Finally, a sensitivity analysis was conducted to determine the potential influence of each study on the overall meta-analysis estimates. This analysis was conducted by recalculating the summary outcome estimates, omitting one study at a time.

RESULTS

Study selection. We screened the abstracts of 265 scientific records for potential inclusion in this meta-analysis. A detailed flow diagram of the literature search is shown in Fig 1. Of these records, 252 citations were irrelevant or incomplete and were excluded from the next stage of analysis. Thus, 13 studies were assessed for eligibility, and the full-text publications were analyzed. Of these publications, seven full-text articles were excluded because the inclusion criteria were not met. Finally, six prospective randomized trials were included in the meta-analysis.

Risk of bias. We assessed the bias risk of the included trials using the Cochrane Collaboration's tool (Table I). All included trials were published prospective randomized clinical trials. The sequence generation method was described adequately and indicated a low risk of bias in all trials except one. The methods of allocation concealment, blinding, and incomplete outcome data were described in almost half of the trials, which indicated a low risk of bias. Most of the trials reported outcomes in a predefined way in the methods sections, which indicated a low risk of bias. Information on other sources of bias was not described in detail in most of the trials. Losses to follow-up were reported in all trials. Intention-to-treat analysis was used in all the trials.

Baseline characteristics. The main demographic and clinical features of the included trials are shown in Table II. The primary and secondary outcomes of the selected studies are presented in Table III. The enrolled patients were predominantly men, elderly, and with

Table II. Main features of included trials

	Rand 2006		*Bosiers 2009*		*Randon 2010*	
	PTA (n = 27)	*Stent (n = 24)*	*PTA (n = 57)*	*Stent (n = 60)*	*PTA (n = 22)*	*Stent (n = 16)*
Age, years	72	72	73.1 ± 8.5	74.7 ± 7.8	72 ± 10	72 ± 9
Male gender	NA	NA	41 (71.9%)	31 (51.7%)	14 (63.6%)	6 (37.5%)
DM	19 (70%)	16 (67%)	39 (68.4%)	43 (71.7%)	12 (55%)	10 (63%)
CAD	11 (41%)	9 (38%)	NA	NA	18 (82%)	12 (75%)
CKD	3 (11%)	5 (21%)	NA	NA	12 (55%)	5 (31%)
Smoking	17 (63%)	14 (58%)	26 (45.6%)	24 (40%)	4 (18%)	1 (6%)
Hypertension	NA	NA	51 (89.%)	51 (85%)	22 (100%)	16 (100%)
Dyslipidemia	NA	NA	35 (61.4%)	32 (53.3%)	9 (41%)	7 (44%)
Type of balloon/stent	Non-drug eluting	Carbofilm coated	Non-drug eluting	Absorbable metal	Non-drug eluting	Bare metal
Lesion length, mm	24.0		12.0 ± 5.0	10.6 ± 4.9	NA	NA
Inclusion criteria	Fontaine III and IV; stenosis >70% or occlusion; lesions ≤3, lesion length ≤3 cm; cumulative lesion length ≤9 cm		Rutherford 4 and 5; stenosis >50% or occlusion; life expectancy >6 months; vessel diameter 3-3.5 mm		Fontaine III and IV; Rutherford 4 to 6; stenosis >70% or occlusion	
Exclusion criteria	Inflow or outflow obstruction; coagulopathy; peptic ulcer; inflammatory vascular disease		Inflow obstruction; previous treatment; allergy to antiplatelet or anticoagulant; participation in another clinical trial; pregnant; mentally ill or retarded		Inflow obstruction; acute limb ischemia; myocardial infarction; blue toe syndrome; inability to ambulate	
Angiographic follow-up/time	Yes/6 months		Yes/6 months		Yes/3, 6, 12, 18, 24 months	

CAD, Coronary artery disease; *CKD,* chronic kidney disease; *DM,* diabetes mellitus; *DVT,* deep venous thrombosis; *NA,* not reported; *PTA,* percutaneous transluminal angioplasty.

Table III. Primary and secondary end points

	Rand 2006		*Bosiers 2009*		*Randon 2010*
	PTA	*Stent*	*PTA*	*Stent*	*PTA*
Technical success	26/27 (96.3%)	23/24 (95.8%)	NA	NA	20/22 (90.9%)
Lost to follow-up	7/27 (25.9%)	7/24 (19.2%)	17/57 (29.8%)	22/60 (36.7%)	0/22 (0%)
Primary patency at 6 months	12/20 (61.1%)	14/17 (83.7%)	35/40 (88.1%)	30/37 (80.2%)	17/22 (76%)
Primary patency at 12 months	NA	NA	NA	NA	15/22 (66%)
Secondary patency at 12 months	NA	NA	NA	NA	17/22 (79.5%)
Clinical improvement at 12 months	NA	NA	NA	NA	NA
Limb salvage at 6 months	20/21 (95%)	17/19 (92%)	53/57 (92.4%)	53/60 (87.6%)	20/22 (90%)
Limb salvage at 12 months	NA	NA	NA	NA	20/22 (90%)
Patient survival at 6 months	26/27 (96.3%)	23/24 (95.8%)	53/57 (92.5%)	55/60 (91.3%)	21/22 (94%)
Patient survival at 12 months	NA	NA	NA	NA	15/22 (69.3%)

NA, Not reported; *PTA,* percutaneous transluminal angioplasty.
[a]Data at 9 months.
[b]Data at 3 months.

coronary artery disease risk factors such as diabetes mellitus, chronic kidney disease, smoking, hypertension, and dyslipidemia. Within each trial, the baseline characteristics were similar between the PTA and stent groups. A total of 548 patients constituted our final study population, with 284 patients (51.8%) treated by PTA and 264 patients (48.2%) treated by primary stenting. The number of participants in the included studies varied from 38 to 200 in the randomized trials. Patients from the study of Rand 2006 were not included in the study of Rand 2011, and patients from the study of Bosiers 2009 were also not included in the study of Scheinert 2012. The disease severity was almost the same, and the main inclusion criteria were Fontaine stages III and IV or Rutherford stages 3 to 5. Four studies reported patients with CLI.[10-13] No significant discrepancies in these criteria were identified among the studies. The main exclusion criteria in the included trials were inflow or outflow obstruction, hematologic diseases, and short life expectancy. The type of stents used in the endovascular procedures varied among the studies and included Carbofilm-coated stents,[14] absorbable metal stents,[10] self-expandable stents,[11] balloon-expandable stents,[12] dedicated stents for below-the-knee arteries,[13] and sirolimus-eluting stents.[15] The types of balloons used in PTA in these trials are all non-drug-eluting balloons. The primary patency rate was defined as restenosis of more than 50% after revascularization or absence of clinically driven target

Table II. Continued.

Brodmann 2011		*Rand 2011*		*Scheinert 2012*	
PTA (n = 33)	*Stent (n = 21)*	*PTA (n = 44)*	*Stent (n = 44)*	*PTA (n = 101)*	*Stent (n = 99)*
68.9 ± 2.9	74.9 ± 1.3	72.1 ± 9.5	71.4 ± 8.0	74.3 ± 8.2	72.4 ± 9.4
13 (39.4%)	12 (57.1%)	28 (63.6%)	30 (68.2%)	76 (75.2%)	67 (67.7%)
24 (72.7%)	16 (76.2%)	34 (75.6%)	35 (79.5%)	65 (64.4%)	64 (64.6%)
29 (87.9%)	18 (85.7%)	NA	NA	45 (44.6%)	45 (45.5%)
NA	NA	NA	NA	NA	NA
8 (24.2%)	7 (33.3%)	NA	NA	27 (26.3%)	38 (38.4%)
27 (81.8%)	19 (90.5%)	NA	NA	92 (91.1%)	89 (89.9%)
6 (18.2%)	14 (66.7%)	NA	NA	69 (68.3%)	77 (77.6%)
Non-drug eluting	Silicon carbide coated	Non-drug eluting	Turbostatic carbon coated	Non-drug eluting	Sirolimus coated
78.48	27.86	20.7 ± 20.1	21.0 ± 12.2	26.8 ± 21.3	26.9 ± 20.9
Rutherford 4 to 6; stenosis >70%, cumulative lesion length ≤12 cm; life expectancy ≥12 months		Rutherford 4 and 5; stenosis ≥50%; lesion length ≤4.5 cm; vessel diameter 2-4 mm		Rutherford 3 to 5	
Inflow obstruction; previous treatment; allergy to clopidogrel or aspirin; indication for oral anticoagulation; participation in another clinical trial		Inflow or outflow obstruction; previous treatment; underlying disease (eg, renal failure or bleeding disorders)		Inflow or outflow obstruction; thrombolysis within 72 hours; DVT; thrombus; life expectancy <12 months; intolerance to antiplatelet; kidney dysfunction	
Yes/3, 6, 12 months		Yes/3 months, 9 months		Yes/6 weeks, 6 months, 12 months	

Table III. Continued.

Randon 2010	*Brodmann 2011*		*Rand 2011*		*Scheinert 2012*	
Stent	*PTA*	*Stent*	*PTA*	*Stent*	*PTA*	*Stent*
14/16 (87.5%)	NA	NA	42/44 (95.5%)	44/44 (100%)	93/101 (92.1%)	95/99 (95.5%)
0/16 (0%)	6/33 (18.2%)	4/21 (19.0%)	18/44[a] (40.9%)	23/44[a] (52.3%)	18/101 (17.8%)	20/99 (20.2%)
13/16 (80%)	16/27 (60.7%)	9/17 (52.6%)	NA	NA	NA	NA
9/16 (56%)	13/27 (48.1%)	6/17 (35.3%)	17/26[a] (65.4%)	16/21[a] (76.2%)	44/77 (57.1%)	54/72 (75%)
10/16 (64%)	19/27 (70.4%)	9/17 (52.9%)	NA	NA	NA	NA
NA	22/27 (81.5%)	11/17 (64.7%)	14/24[a] (58.3%)	9/19[a] (47.4%)	51/76 (67.1%)	54/71 (76.1%)
15/16 (91.7%)	NA	NA	28/32[b] (87.5%)	27/33[b] (81.8%)	NA	NA
15/16 (91.7%)	NA	NA	19/26[a] (73%)	11/21[a] (52.4%)	68/85 (80%)	69/80 (86.3%)
13/16 (79.8%)	NA	NA	41/44[b] (93.2%)	39/44[b] (88.6%)	NA	NA
12/16 (74.7%)	27/33 (81.8%)	18/21 (85.7%)	39/44[a] (88.6%)	39/44[a] (88.6%)	89/101 (88.1%)	89/99 (89.9%)

lesion revascularization. Secondary patency was defined as freedom from repeated angioplasty until recurrence of symptoms.

Outcomes

The meta-analysis outcomes in the entire study population are summarized in the Table IV. The random-effects model was used only in the analysis of primary patency at 12 months because of the heterogeneity that existed. Begg test and Egger test validated the absence of publication bias. The eight summary ORs of combined parameters were of no statistical significance.

Technical success. Four trials[11,13-15] evaluated the technical success of PTA vs stenting. The incidence of combined technical success was 93.3% in the PTA group and 96.2% in the stent group. There was no significant difference between the two groups, and the summary OR was 0.59 (95% CI, 0.24-1.47; $Z = 1.14$; $P = .25$). There was low heterogeneity across the trials ($\chi^2 = 1.51$; $P = .68$; $I^2 = 0\%$). The funnel plot, Begg test ($Z = 0.34$; $P = .743$), and Egger test ($t = 0.19$; $P = .869$) indicated no publication bias among the trials (Fig 2).

Primary patency. Four trials[10,11,13,14] evaluated the primary patency at 6 months for PTA vs stenting. The incidence of combined primary patency at 6 months was 73.4% in the PTA group and 75.9% in the stent group. There was no significant difference between the two groups, and the summary OR was 0.94 (95% CI, 0.48-1.8; $Z = 0.18$; $P = .86$). There was low heterogeneity across the trials ($\chi^2 = 2.94$; $P = .40$; $I^2 = 0\%$). The funnel plot, Begg

Table IV. Summary meta-analysis of outcomes in the entire study population

Outcome measure	*No. of studies*	*Meta-analysis model*	*OR (95% CI)*	P	*Publication bias* (P)
Technical success	4	Fixed effects	0.59 (0.24-1.47)	.25	.869
Primary patency at 6 months	4	Fixed effects	0.94 (0.48-1.83)	.86	.202
Primary patency at 12 months	3	Random effects	0.95 (0.35-2.58)	.92	.453
Patient survival at 6 months	3	Fixed effects	0.96 (0.29-3.18)	.95	.805
Patient survival at 12 months	3	Fixed effects	0.79 (0.40-1.55)	.49	.199
Limb salvage at 6 months	3	Fixed effects	1.55 (0.56-4.29)	.40	.741
Limb salvage at 12 months	2	Fixed effects	0.64 (0.29-1.41)	.27	NA
Secondary patency at 12 months	2	Fixed effects	2.08 (0.81-5.34)	.13	NA

CI, Confidence interval; *NA,* not applicable; *OR,* odds ratio.

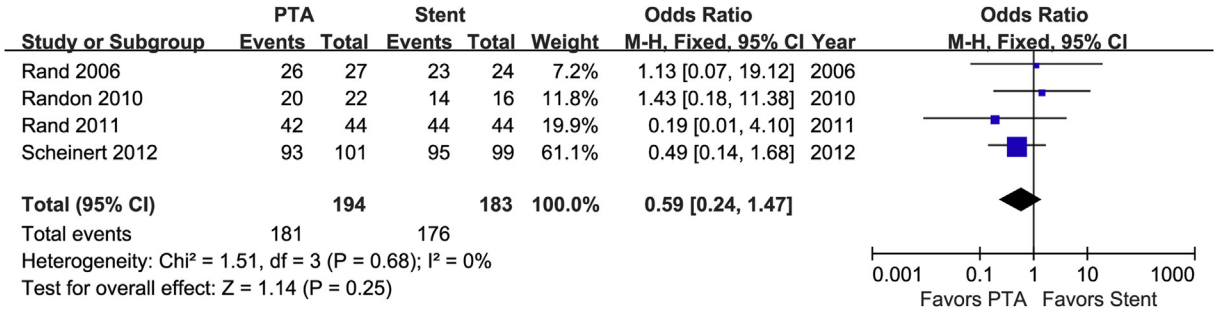

Fig 2. Forest plot of the estimated individual and overall effect of the technical success at 12 months between percutaneous transluminal angioplasty (*PTA*) and primary stenting groups. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

test ($Z = 0.34$; $P = .743$), and Egger test ($t = -1.87$; $P = .202$) indicated no publication bias among the trials (Fig 3).

Three trials[11,12,15] evaluated the primary patency at 12 months for PTA vs stenting. The incidence of combined primary patency at 12 months was 57.1% in the PTA group and 65.7% in the stent group. There was high heterogeneity across the trials ($\chi^2 = 5.17$; $P = .08$; $I^2 = 61\%$). Therefore, we used a random-effects model to calculate the combined parameters. There was no significant difference between the two groups, and the summary OR was 0.95 (95% CI, 0.35-2.58; $Z = 0.10$; $P = .92$). The funnel plot, Begg test ($Z = 0.00$; $P = 1.00$), and Egger test ($t = 1.16$; $P = .453$) indicated no publication bias among the trials (Fig 3).

Secondary patency. Only two trials[11,12] evaluated the secondary patency at 12 months for PTA vs stenting. The incidence of combined secondary patency at 12 months was 73.5% in the PTA group and 57.6% in the stent group. There was no significant difference between the two groups, and the summary OR was 2.08 (95% CI, 0.81-5.34; $Z = 1.52$; $P = .13$). There was low heterogeneity across the trials ($\chi^2 = 0.00$; $P = .97$; $I^2 = 0\%$) (Fig 4). No available data were found to evaluate secondary patency at 6 months in these trials.

Limb salvage. Three trials[10,11,14] evaluated limb salvage at 6 months for PTA vs stenting. The incidence of combined limb salvage at 12 months was 93.0% in the PTA group and 89.5% in the stent group. There was no significant difference between the two groups, and the summary OR was 1.55 (95% CI, 0.56-4.29; $Z = 0.85$; $P = .40$). There was low heterogeneity across the trials ($\chi^2 = 0.58$; $P = .75$; $I^2 = 0\%$). The funnel plot, Begg test ($Z = 0.00$; $P = 1.000$), and Egger test ($t = -0.43$; $P = .741$) indicated no publication bias among the trials (Fig 5).

Only two trials[11,15] evaluated limb salvage at 12 months for PTA vs stenting. The incidence of combined limb salvage at 12 months was 82.2% in the PTA group and 87.5% in the stent group. There was no significant difference between the two groups, and the summary OR was 0.64 (95% CI, 0.29-1.41; $Z = 1.11$; $P = .27$). There was low heterogeneity across the trials ($\chi^2 = 0.00$; $P = .97$; $I^2 = 0\%$).

Patient survival. Three trials[10,11,14] evaluated the patient survival at 6 months for PTA vs stenting. The incidence of combined patient survival at 6 months was 94.3% in the PTA group and 94.8% in the stent group. There was no significant difference between the two groups, and the summary OR was 0.96 (95% CI, 0.29-3.18; $Z = 0.06$; $P = .95$). There was moderate heterogeneity across the trials ($\chi^2 = 3.30$; $P = .19$; $I^2 = 39\%$). The funnel plot, Begg test ($Z = 0.00$; $P = 1.000$), and Egger test ($t = 0.32$; $P = .805$) indicated no publication bias among the trials (Fig 6).

Three trials[11,12,15] evaluated the patient survival at 12 months for PTA vs stenting. The incidence of combined

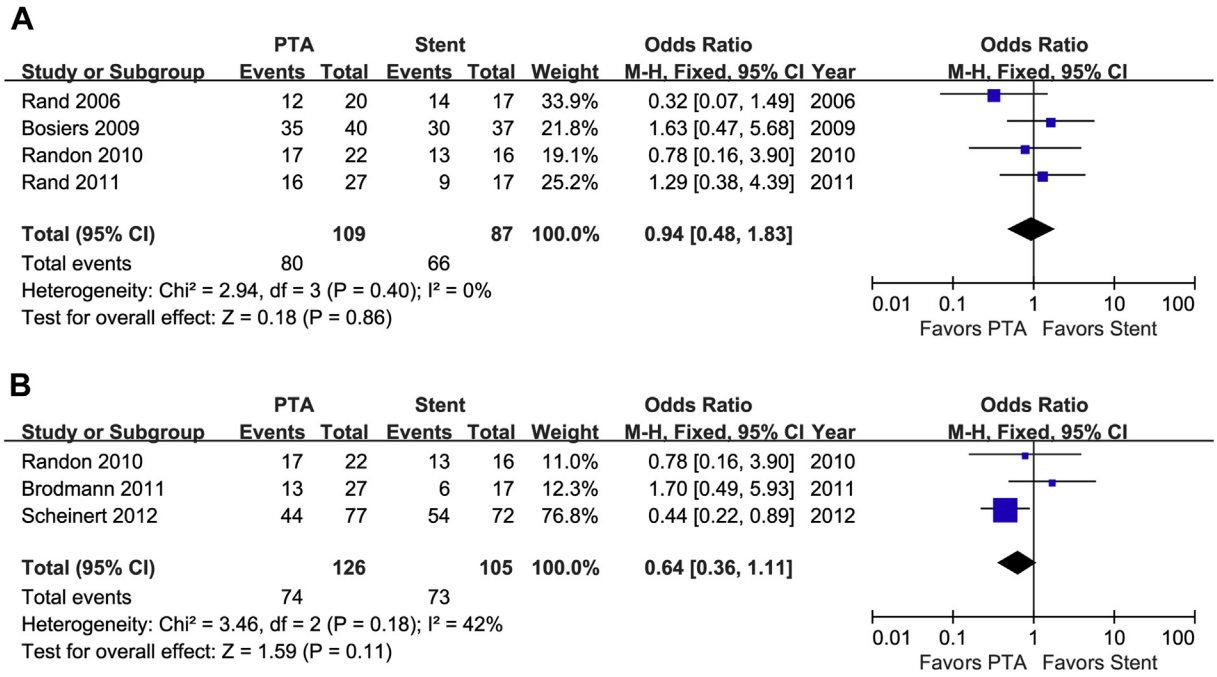

Fig 3. Forest plots of the estimated individual and overall effect of the primary patency between percutaneous transluminal angioplasty (*PTA*) and primary stenting groups at 6 months **(A)** and 12 months **(B)**. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

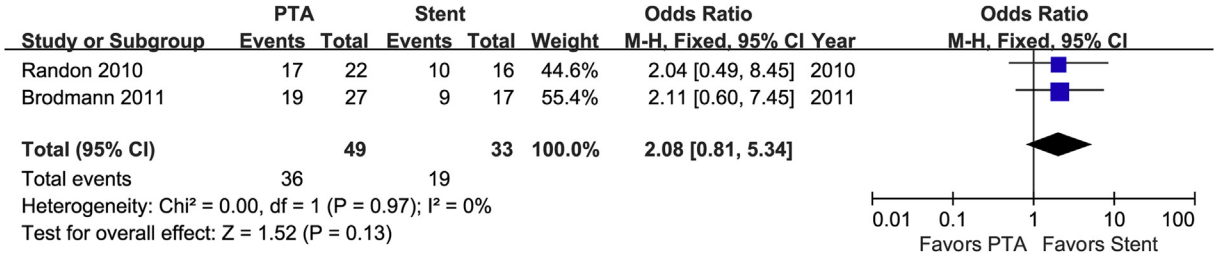

Fig 4. Forest plot of the estimated individual and overall effect of the secondary patency at 12 months between percutaneous transluminal angioplasty (*PTA*) and primary stenting groups. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

patient survival at 12 months was 84.0% in the PTA group and 87.5% in the stent group. There was no significant difference between the two groups, and the summary OR was 0.79 (95% CI, 0.40-1.55; $Z = 0.69$; $P = .49$). There was low heterogeneity across the trials ($\chi^2 = 0.04$; $P = .98$; $I^2 = 0\%$). The funnel plot, Begg test ($Z = 0.00$; $P = 1.000$), and Egger test ($t = -3.10$; $P = .199$) indicated no publication bias among the trials (Fig 6).

Sensitivity analysis

Sensitivity analyses were performed to determine the influence of a single study on the overall effect estimate. The pooled estimates for technical success, primary patency, secondary patency, limb salvage, and patient survival were recalculated and omitted one study at a time. The results showed that no single study significantly influenced the summary ORs of the end points because every outcome point estimate was within the initial 95% CI when one study was omitted at a time.

DISCUSSION

The continuous advancement of endovascular technology and equipment has revolutionized the treatment of lower extremity arterial occlusive disease in the last decades.[16-18] Physicians should find an optimal treatment strategy through comparing the therapeutic effects of this technology and equipment and then propagate the use of it. Infrapopliteal intervention is different from intervention for more proximal arteries in several aspects.[19] Arteries below the knee are smaller in caliber and often have severe calcification, especially in patients with CLI.[20,21] CLI associated with infrapopliteal arteries often involves long

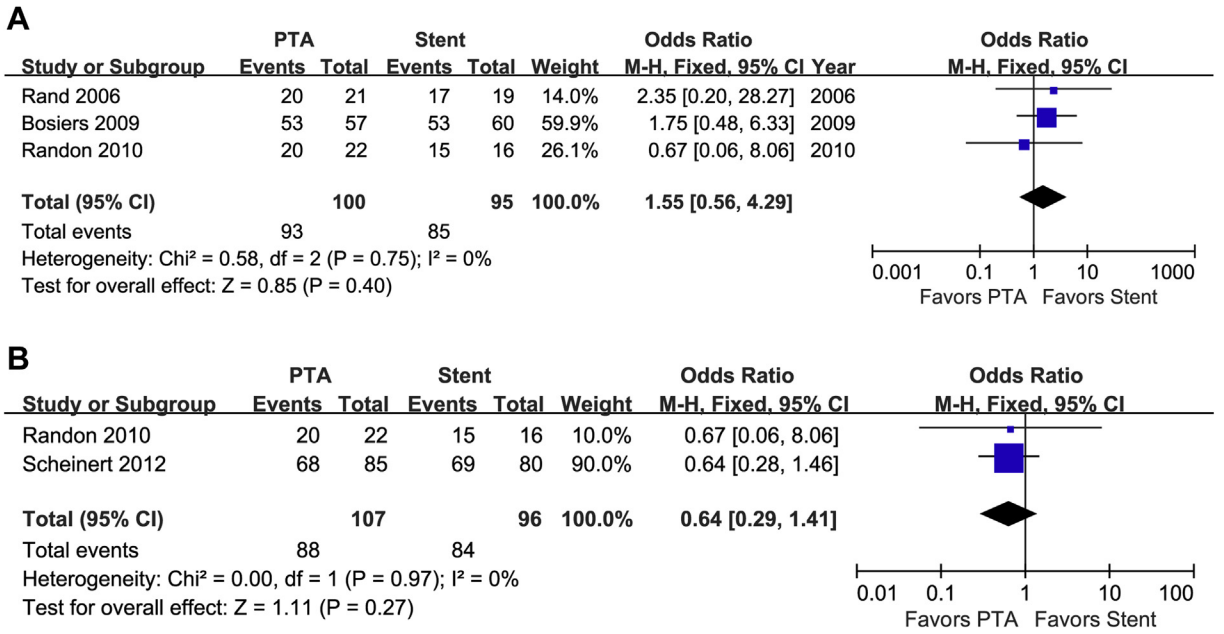

Fig 5. Forest plots of the estimated individual and overall effect of the limb salvage between percutaneous transluminal angioplasty (*PTA*) and primary stenting groups at 6 months **(A)** and 12 months **(B)**. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

segments and even extends diffusely into three vessels. Only 20% to 30% of cases have simple focal lesions and good runoff.[22] Patients who are elderly, suffer from severe comorbidities, and have a limited life expectancy will have the worst prognosis.[23-25] Therefore, the endovascular treatment of the infrapopliteal arteries remains a challenge for physicians. The published data have proved that infrapopliteal PTA is an effective treatment in patients with CLI.[26] It can be used to feasibly and safely treat these patients, with satisfactory clinical results.[26,27] PTA in small-caliber below-the-knee arteries is also accompanied by elastic recoil, arterial remodeling, and dissection, which are caused by technical failure and other complications.[3] Stent implantation, especially of dedicated stents, may reduce these complications and theoretically improves the patency rate.[28] However, its application in the infrapopliteal arteries is still debated. The treatment outcomes of stent implantation in this arterial segment have not reached the initial expectations. The main challenges are the risks of fracture, restenosis, thrombosis, and inflammatory and proliferative responses of the arterial wall.[29,30] Primary stenting means stenting is the first strategy in the treatment of infrapopliteal arterial occlusive diseases, not after failed angioplasty. Until now, a consensus on the benefits of PTA over primary stenting has not been reached. Several recent prospective randomized studies compared the outcomes of PTA vs primary stenting in the treatment of infrapopliteal arterial occlusive disease, but the results were inconsistent.

In this article, we focused on which therapeutic measure is better as the first choice for this kind of disease, angioplasty or primary stenting. To obtain subjective and accurate results, we involved only randomized trials in our analysis. The present meta-analysis of randomized trials was conducted to investigate the outcomes of PTA vs primary stenting in patients undergoing revascularization for infrapopliteal arterial occlusive disease and provided level I evidence-based recommendation about the controversy regarding which method is the optimal first-line treatment in such patients. The results showed that primary stenting did not significantly improve outcomes at 12 months, as expressed by technical success, primary patency, secondary patency, limb salvage, and patient survival. There are several explanations for the findings of the present analysis.

First, the variability of stent types may affect the pooled outcomes. Six different types of stents were used in the included trials. Different stent types may have different therapeutic results in the same disease.[31,32] Some studies demonstrated favorable 1-year results with primary stenting compared with PTA, but other studies did not produce similar results. This difference may have led to the insignificant combined results of the comparisons between the two endovascular procedures. Further trials are needed to focus on a single stent, such as one dedicated for use in infrapopliteal arteries, and then to compare the results of primary stenting vs PTA. A meta-analysis based on such trials may have more authentic results.

Second, our current analysis included six studies with 548 participants. For one of the parameters, not all studies provided information. Some results were based on only two trials with fewer than 200 participants. Thus, the total number of participants enrolled in this meta-analysis was relatively small, which may lead to some bias in the pooled results. The primary patency rates of PTA and primary stenting were 57.1% and 65.7%, respectively. The

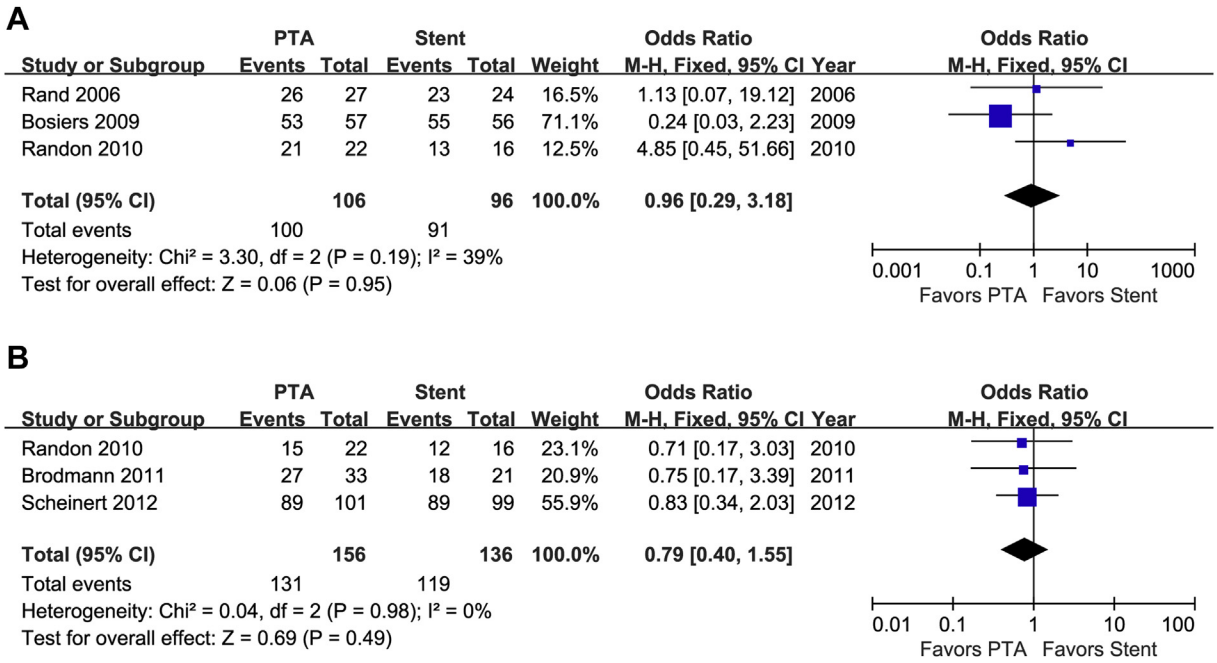

Fig 6. Forest plot of the estimated individual and overall effect of the patent survival between percutaneous transluminal angioplasty (*PTA*) and primary stenting groups at 6 months **(A)** and 12 months **(B)**. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

secondary patency rates were 73.5% and 57.6%, respectively. Although these differences are not significant, primary stenting appeared to be associated with a trend toward higher primary patency and lower secondary patency. Compared with primary stenting, the technical success of revascularization was higher in patients after PTA. Therefore, the secondary patency might be higher. Trials with a larger number of enrolled participants might be able to confirm this result. Meanwhile, the weight percentage of each study in the analysis was unbalanced. In the pooled analysis of primary patency at 12 months, the weight percentage of Scheinert's study, which was 76.8%, was much greater than that of the other studies.[15] This imbalance may be the source of heterogeneity for this outcome. Thus, the results of this analysis were limited. In the future, large-scale prospective randomized trials are expected to obtain more reliable results.

Third, the duration of follow-up was relatively short in the six included trials. All six trials had only 12-month follow-ups; thus, the long-term results remain unknown. Differences in some outcome parameters that were not significant at 12 months might be significant at more than 12 months. Further trials should prolong the follow-up time and evaluate the long-term efficacy of these two endovascular procedures.

Fourth, the length of lesions might influence the therapeutic effect. In five of six trials involved in our meta-analysis, there was no statistically significant difference between the PTA group and the stenting group in the length of lesions. Only in the trial of Brodmann 2011 was the length of lesions in the PTA group significantly longer than in the stenting group. However, the results show that stenting does not outstrip the benefit of PTA.[12] Further study is needed to investigate the role of lesion length in the treatment of infrapopliteal arterial occlusive diseases.

Finally, the outcome parameters used to evaluate the anatomic and clinical results in the meta-analysis may not sufficiently substantiate the clinical effects. Some additional factors, such as freedom from target lesion revascularization, should be introduced to assess the clinical outcomes. Furthermore, in treating complicated lesions, such as multilevel or multilocal disease in CLI patients, the performance of PTA and primary stenting should be further evaluated. Because of these inherent limitations, conclusions about the impact of this meta-analysis on clinical practice should be made carefully.

CONCLUSIONS

This analysis demonstrated that PTA and primary stenting have the same safety and efficacy for the treatment of CLI leading to infrapopliteal arterial occlusive disease. The comparisons of the 12-month results between the two treatment groups related to technical success, primary patency, secondary patency, limb salvage, and patient survival did not reveal any significant differences. Primary stenting is associated with a trend toward higher primary patency and lower secondary patency. There was insufficient evidence to demonstrate that one treatment is better than the other. Further multicenter and prospective randomized trials evaluating the outcomes of PTA and

primary stenting are required to assess the efficacy of the two treatments in patients with infrapopliteal arterial occlusive disease.

AUTHOR CONTRIBUTIONS

Conception and design: CY
Analysis and interpretation: XX
Data collection: SIW
Writing the article: RW
Critical revision of the article: MW
Final approval of the article: SHW
Statistical analysis: RW, ZL
Obtained funding: SHW
Overall responsibility: SHW
RW and CY share co-first authorship for this article.

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